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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,350	08/13/2002	Guillaume Jean Hervieu	P32320	3095

20462 7590 07/27/2004

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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,350	HERVIEU ET AL.	
	Examiner	Art Unit	
	Zachary C Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/14/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-29* is/are pending in the application.

4a) Of the above claim(s) *15,18-21 and 23-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14, 16, 17 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *15, 18-21 and 23-29* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/30/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of claims 14-19 and 22, in so far as they are drawn to methods of treatment by administration of compounds that inhibit an h-TREK polypeptide, in the reply filed on 6/14/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 20-21 and 23-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant's election of the species of sleep-related disorders in the reply filed on 6/14/2004 is acknowledged.

Claims 15, 18 and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 14, 16, 17, and 22 are under consideration.

Objections

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The current title "New use" is

not descriptive because it does not indicate what new use the invention is directed towards.

Claim Objections

Claim 14 is objected to because the claim encompasses non-elected inventions and non-elected species. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 16, 17 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 14, 16, 17 and 22 are drawn to a method of treatment with a compound that inhibits an h-TREK polypeptide. The specification teaches (page 13, lines 19-24) "the present invention provides methods of treating abnormal conditions such as, for

instance, epilepsy, sleep-related disorders, the induction of sleep...related to an excess of, or an under-expression of h-TREK1 polypeptide activity". Page 13, lines 25-30 teach that if "the activity of the polypeptide is in excess, several approaches are available. One approach comprises administering to a subject in need thereof an inhibitor compound (antagonist) as hereinabove described, in an amount effective to inhibit the function of the polypeptide, such as, for example, by blocking the binding of ligands, substrates, receptors, enzymes, etc., or by inhibiting a second signal, and thereby alleviating the abnormal condition." Page 11, lines 3 teach "the present invention provides for a method of screening for compounds which stimulate or inhibit the function of the polypeptide. In general, agonists or antagonists may be employed for therapeutic or prophylactic purposes for such Diseases as hereinbefore mentioned." Immediately following this, the specification provides a list of source of potential compounds which may be screened. Page 12, paragraph 3 further teaches, "Examples of potential polypeptide antagonists include antibodies or in some cases oligonucleotides or proteins which are closely related to the ligands, substrates, receptors, enzymes, etc., as the case may be, of the polypeptide. e.g., a fragment of the ligands, 25 substrates, receptors, enzymes, etc.; or small molecules which bind to the polypeptide of the present invention but do not elicit a response, so that the activity of the polypeptide is prevented". Of these potential inhibitory compounds, only the design of antibodies to block a potassium channel is established in the art (Zhou, et al., 1998, Journal of General Physiology 111:555-563). What is missing from the specification is a disclosure of other specific compounds which will inhibit an h-TREK polypeptide. Without a

disclosure of these compounds the specification lacks adequate written description to support the scope of the claims, and a meaningful search of methods of treatment with these potential compounds cannot be performed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

The skilled artisan cannot envision the chemical structure of compound encompassed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 14, 16, 17, and 22, in so far as they are drawn to methods of treatment of sleep-related disorders by inhibition of an h-TREK polypeptide, are rejected under 35

U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method of treatment of a sleep-related disorder by administration of a compound which inhibits a human TREK-1 polypeptide.

The prior art teaches that mouse TREK-1 is two-P-domain potassium channel (Fink, et al, 1996. Cited as Reference AB in the IDS of 11/30/2001). Human TREK-1 has been cloned and reported to have similar biophysical properties to mouse TREK1 (Meadows, et al, published 7/29/1999. Cited as Reference AA in the IDS of 11/30/2001). Human and mouse TREK-1, as with most 2-P-domain potassium channels, are potassium leak channels which are the responsible for the leak currents which "exert control over excitability by shaping the duration, frequency and amplitude

of action potentials" (Goldstein, et al, 2001, Nature Reviews Neuroscience 2(3): 175-184).

Goldstein further summarizes (on page 180) the connection between neurotransmitter-inhibited potassium leak channels and the sleep-wake cycle: "inhibition of resting K+ leak currents is a widespread mechanism by which serotonin, noradrenaline, substance P, glutamate, thyrotropin-releasing hormone (TRH) and acetylcholine (acting through muscarinic receptors) enhance neuronal excitability in the nervous system. This is crucial to the regulation of 'state-switching' in cortical and thalamic neurons, which seems to mediate transitions between sleep and wakefulness, and perhaps attentiveness." As of July 2003, the connection between particular 2-P-domain channels and activity modes in the thalamocortical network was not known (Meuth, et al, 2003, Journal of Neuroscience, 23(16): 6460-6469). Meuth (in the Abstract) teaches: "The thalamocortical network is characterized by a rhythmic burst activity during natural sleep and tonic single-spike activity during wakefulness. The change between these two activity modes is partially governed by transmitters acting on leak K+ currents in the thalamus, although the nature of the constituting ion channels in not yet known." Meuth further (entire paper) teaches the contribution of two members of the 2-P-domain channel family, TASK1 and TASK3, to the leak current in thalamocortical relay neurons. Meuth demonstrates expression of TASK1 and TASK3 genes in these neurons through RT-PCR (Figure 1) and demonstrates the contribution of TASK1 and TASK3 to leak K+ currents by (as taught in Figures 2-9 and summarized in the Abstract): "Voltage-clamp recordings of thalamocortical relay neurons in slice

preparations demonstrated the existence of a current component sensitive to the TASK channel blocker bupivacaine, which reversed at the presumed K+ equilibrium potential, showed outward rectification, and contributed approximately 40% to the standing outward current at depolarized values of the membrane potential (-28 mV). The pharmacological profile was indicative of TASK channels, in that the current was sensitive to changes in extracellular pH, reduced by muscarine and increased by halothane, and these effects were occluded by a near-maximal action of bupivacaine. Pharmacological manipulation of this current under current-clamp conditions resulted in a shift between burst and tonic firing modes. It is concluded that TASK1 and TASK3 channels contribute to the muscarine- and halothane-sensitive conductance in thalamocortical relay neurons, thereby contributing to the change in the activity mode of thalamocortical networks observed during the sleep-wake cycle and on application of inhalational anesthetics."

To date, no art has demonstrated that h-TREK1 contributes to the leak current in neurons associated with induction of sleep. The specification does not provide sufficient guidance to practice the claimed invention without undue experimentation. The specification teaches (page 13, lines 19-24) "...the present invention provides methods of treating abnormal conditions such as, for instance, epilepsy, sleep-related disorders, the induction of sleep...related to an excess of, or an under-expression of h-TREK1 polypeptide activity" and teaches methods of screening for compounds which inhibit an h-TREK polypeptide. However, nowhere does the specification teach that a sleep-related disorder is actually related to an excess of h-TREK1 polypeptide activity. The

nexus between h-TREK1 polypeptide activity and sleep is speculation based on localization data. The specification states: (starting on page 1, line 28) "...h-TREK is highly expressed on a number of GABA-ergic cells of the reticular thalamic nucleus. The reticular thalamic nucleus plays an important role in the transition from wakefulness to sleep by inhibiting via GABA-ergic projections the activity of other thalamic nuclei. Thus an h-TREK1 channel modulator, preferably an antagonist, could alter alertness and may facilitate the transition from wakefulness to sleep or vice-versa."

The localization of h-TREK1 polypeptide in the reticular thalamic nucleus does not predict that activity of the h-TREK1 polypeptide contributes to induction of sleep. Goldstein indicates that there are at least 11 2P potassium channels in humans that are differentially regulated by kinase-dependent pathways, arachidonic acid, membrane stretch, external pH, and temperature (Table 1). TASK1 and TASK3 channels are acid-sensitive while the TREK1 channels are not, which demonstrates differences in the regulation of these channels and indicates the results of Meuth can not necessarily be extrapolated to h-TREK1. Due to the level of unpredictability in the art, experimentation with h-TREK1 such as provided by Meuth for TASK1 and TASK3 is necessary to establish a nexus between an ion channel and leak K+ currents in neurons associated with induction of sleep. Claims 14 and 16 encompass disorders of any type that affect sleep, from narcolepsy to insomnia, and everything in between, and it is unlikely that both conditions could be treated by inhibiting h-TREK1.

The quantity of experimentation needed to make and use the invention as claimed would be undue because a person of skill in the art would need to confirm a

nexus between h-TREK polypeptide activity and induction of sleep, screen for compounds which inhibit h-TREK activity, and then test whether the compounds would induce sleep in subjects. Administration of the compounds is also an issue; if the compounds would not pass the blood-brain barrier they would have to be injected into the brain of subjects, which seems like an unsuitable method for induction of sleep.

Conclusion

The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon for a rejection are considered pertinent to the instant application:

a. U.S. Patent 6,242,217, filed 1/25/99 (and claiming priority to EP98300570 1/27/1998) discloses and claims h-TREK1 polypeptides and nucleotides, discloses (column 12 lines 5-35 methods) of screening for antagonists of h-TREK1 polypeptides, and discloses (column 12 lines 36-58) using methods of treatment of conditions where "...the activity of the polypeptide is in excess..." by "administering to a subject in need thereof an inhibitor compound (antagonist)..." Specific antagonists with h-TREK1 inhibitory activity are not disclosed.

b. U.S. Publication No. US20030036648A1, filed 6/18/2002 (and claiming priority to 8/7/1998) teaches an amino acid sequence, SEQ ID NO: 83, which shares 100% homology to the instantly claimed SEQ ID NO: 2, but does not teach methods of treatment of sleep-related disorders with a compound which inhibits h-TREK1 polypeptide activity.

c. WO9943696-A1, published 9/2/1999 (and claiming priority to 8/7/1998) teaches in Claim 3; page 104-105 an amino acid sequence which shares 100% homology to the instantly claimed SEQ ID NO: 2, but does not teach methods of treatment of sleep-related disorders with a compound which inhibits h-TREK1 polypeptide activity.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:00 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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